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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte WEIHONG XIONG and DINESH C. PATEL

Appeal 2009-014788[1]
Application 10/723,435
Technology Center 1600

Before TONI R. SCHEINER, MELANIE L. McCOLLUM, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

DECISION ON APPEAL[2]

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims directed to a method of improving cognitive function. The claims have been rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

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[1] Heard October 14, 2010.

[2] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52, begins to run from the "MAIL DATE" (paper delivery mode) or the "NOTIFICATION DATE" (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

STATEMENT OF THE CASE

According to the Specification,

> Huperzine is a natural, potent, and selective cholinesterase inhibitor . . . found in the club moss *Huperzia Serrata*, also known as *Quian Ceng Ta*, and has been used for centuries in Chinese herbal medicine to treat a variety of ailments and disorders such as fever and inflammation. Huperzine has also been prescribed in China for the amelioration of memory loss, dementia, and cognitive function disorders.

(Spec. 5: 2-9.)

Claims 81-84, 86, 102, and 103 are pending and on appeal.[3] The claims have not been argued separately, therefore, we select claim 81 as representative, and the remaining claims will stand or fall according to claim 81. 37 C.F.R. § 41.37(c)(1)(vii). Claim 81 is as follows:

81. A method of improving memory and cognitive function in a subject, comprising:

transdermally administering huperzine to the subject from a transdermal matrix patch that includes an adhesive matrix with an acrylate polymer including homopolymers, copolymers, or terpolymers, or rubber-based pressure sensitive adhesive including copolymers and a fatty acid ester of lactic acid as a permeation enhancer, said matrix patch excluding Azone, in order to provide a huperzine blood plasma level of from about 0.1 to about 30 ng/ml for a duration of at least about 3 days from a single transdermal administration.

The claims stand rejected under 35 U.S.C. § 103(a) as unpatentable over Hwang[4] and Venkateshwaran.[5]

We affirm.

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[3] Claims 53-80 and 87-97 are also pending, but have been withdrawn from consideration; claims 1-52, 85, and 98-101 have been canceled (App. Br. 5).

[4] U.S. Patent 6,352,715 B1, issued March 5, 2002 to Hwang et al.

[5] U.S. Patent 6,365,178 B1, issued April 2, 2002 to Venkateshwaran et al.

FINDINGS OF FACT

1. Claim 81 is directed, in pertinent part, to a method of improving cognitive function in a subject by administering huperzine to the subject through a transdermal matrix patch in order to provide a huperzine blood plasma level of from about 0.1 to about 30 ng/ml for a duration of at least about 3 days from a single transdermal administration, where the transdermal patch comprises an adhesive matrix, e.g., an acrylate polymer, and a fatty acid ester of lactic acid, i.e., a permeation enhancer.

2. The Specification defines a transdermal matrix patch as "a pre-determined amount of huperzine dissolved or suspended in a polymeric carrier or phase, in one aspect a pressure-sensitive adhesive . . . in which a permeation enhancer . . . may also [be] dissolved or suspended" (Spec. 17: 12-18). The matrix patch may also have an impermeable film backing (*id.* at 17: 22-23).

3. The Specification teaches that "acceptable adhesives may include polyacrylate polymers" which "can be any of the homopolymers, copolymers, terpolymers . . . of various acrylic acids" (Spec. 33: 18-22).

4. According to the Specification:

> The time frame for achieving [desired] blood plasma levels may be the result of such parameters as the type and size of the huperzine formulation, the amount of huperzine present in the formulation, and the flux rate achieved by the formulation. Further, the flux rate may be determined in part by the presence of specific types of penetration enhancers.

(Spec. 21: 16-21.)

5. The Specification teaches that:

> A wide range of known permeation enhancers have been found to enhance the delivery of huperzine and include but are not

> limited to: fatty acids, fatty acid esters, fatty alcohols, fatty acid esters of lactic acid or glycolic acid and their salts, amides, amines, pyrrolidones, glycerol triesters, terpenes, classical surfactants, organic acids, complexing agents, biologics, and mixtures thereof.

(Spec. 23: 13-19.)

6. On the other hand, the Specification also teaches that "no enhancer is necessary in order to achieve the desired blood plasma levels in many instances," thus, a transdermal formulation may "consist essentially of an amount of huperzine sufficient to achieve a huperzine blood plasma level of from about 0.1 to about 30 ng/ml admixed with an inert carrier" (Spec. 10: 5-11).

7. The Specification teaches that "the huperzine is administered in an amount sufficient to affect and maintain a blood plasma level of about 0.1 ng/mL to about 30 ng/mL" (Spec. 21: 11-13), and "permeation rates of huperzine through living human skin may be in the range of about 0.01 $\mu g/cm^2/hr$ to about 15 $\mu g/cm^2/hr$" (*id.* at 22: 6-9).

8. Hwang describes "an adhesive-type transdermal drug delivery device suitable for transdermal administration of [huperzine] to provide therapeutical benefits to patients with Alzheimer disease" (Hwang, col. 3, ll. 7-10).

> [T]he adhesive-type transdermal drug delivery device comprises (i) a concentration of [huperzine] in an amount sufficient to enable said [huperzine] to exhibit anti-Alzheimer activity through said transdermal administration; (ii) at least a pressure-sensitive adhesive polymer in a concentration sufficient to dissolve said [huperzine] to [form] a [huperzine] adhesive solution in presence of an organic solvent; and (iii) a sheet of drug-impermeable backing laminate . . .

(*id.* at col. 3, ll. 10-18).

9. Hwang teaches that an adhesive-type transdermal delivery device can be prepared by dissolving a dosage amount of huperzine in HY-3, a pressure-sensitive polyacrylate adhesive, and a combination of organic solvents; casting the huperzine solution onto a sheet of drug-impermeable backing laminate, removing the organic solvents, and cutting the coated sheet into 10 cm^2 pieces (Hwang, col. 9, ll. 31-66). In a specific example, 2.25% huperzine by weight was dissolved in HY-3 to form a uniform solution which was cast into a 75 μm thick film and cut into 2 cm patches (surface area 3.14 cm^2), to obtain a loading dose of about 1 mg huperzine per patch (*id.* at col. 10, ll. 35; Table 2).

10. Hwang's "adhesive-type transdermal drug delivery device" is a "matrix patch," as that term is defined in the present Specification (compare FF2, FF8, and FF9).

11. Release of huperzine from Hwang's HY-3 containing delivery device "was found to follow a linear square root of time profile till over 60% of drug were released, followed by a slower phase" and "[t]he transdermal permeation profile was found to show linearity for up to at least 7 days" (Hwang, col. 13, ll. 56-60). "The drug release rate obtained over 7 days was 1.39 (+-0.15) $\mu g/cm^2.h$, which is higher than the estimated required rate of 0.833 $\mu g/cm^2.h$ using a 10 cm^2 patch" (*id.* at col. 13, ll. 62-64).

12. Hwang teaches that "[t]he permeation rate required to achieve the therapeutic levels of [huperzine] by transdermal delivery is calculated to be 4.2 $\mu g/cm^2/hr$ if a 10 cm^2 patch is used. A reservoir formulation or using a combination of co-solvents to increase the skin permeability of neutral [huperzine] could be a viable approach" (Hwang, col. 8, ll. 62-67).

13. Venkateshwaran teaches that typical polymers used as pressure sensitive adhesives in transdermal matrix patches include natural rubbers and polyacrylates (Venkateshwaran, col. 6, ll. 41-45). Venkateshwaran also teaches that permeation enhancers include saturated and unsaturated fatty acids and their esters, alcohols, monoglycerides, acetates, etc. (*id* at col. 7, ll. 45-67).

14. Venkateshwaran describes an adhesive matrix patch containing an acidic drug (diclofenac sodium) or a basic drug (buspirone HCl or clonidine HCl) combined with a water-based acrylic adhesive and the permeation enhancer, laurel lactate (an ester of lactic acid and lauryl alcohol) (Venkateshwaran, col. 22, ll. 28-38).

15. Lee,[6] a reference cited by Appellants in their Brief (page 14), teaches that "the behavior of permeation enhancers is highly idiosyncratic; a permeation enhancer effective for one drug may not be effective with other drugs" (Lee, col. 2, ll. 48-52). In addition, Lee teaches:

> Often, a permeation enhancer will exacerbate irritation and sensitization problems by allowing high transdermal permeation rates of the drug or permeation enhancer or permitting otherwise impermeable components of the transdermal device to enter the skin. Many potential permeation enhancers interact adversely with other components of transdermal devices. One major problem is that many potential permeation enhancers are not compatible with medically acceptable contact adhesives . . .
>
> The use of a permeation enhancer in any transdermal drug delivery device necessarily complicates the design and development of the device. Permeation enhancers cause compatibility problems throughout the delivery system. Instead of having to characterize the properties of the reservoir

[6] U.S. Patent 5,500,222, issued March 19, 1996 to Lee et al.

> compositions, adhesives, and release-controlling materials with respect to just the drug, these materials must now have the proper characteristics with respect to both the drug and the permeation enhancer. Typically, drugs and permeation enhancers have very different physical and chemical properties, and, in most cases, the properties of mixtures of the drug with the permeation enhancer are unknown. For example, permeation enhancers can cause, among other problems, cohesive failure of adhesives and can partition through other components in the system.

(*Id.* at col. 2, l. 54 to col. 3, l. 12.)

16. Similarly, Carrara,[7] another reference cited by Appellants in their Brief (page 15), teaches:

> It is often difficult to predict which compounds will work as permeation enhancers and which permeation enhancers will work for particular drugs. In transdermal drug delivery applications, a compound that enhances the permeability of one drug or a family of drugs may not necessarily enhance the permeability of another drug or family of drugs. . . .
>
> Therefore, the usefulness of a particular compound(s) or mixture thereof as a permeation enhancer must be carefully analyzed and demonstrated by empirical work.

(Carrara, col. 2, ll. 8-20.)

DISCUSSION

Claim 81 is directed to a method of improving cognitive function in a subject by administering huperzine to the subject through a transdermal matrix patch to provide a huperzine blood plasma level of from about 0.1 to about 30 ng/ml for at least about 3 days from a single administration, where the transdermal patch comprises an adhesive matrix, e.g., an acrylate polymer, and a fatty acid ester of lactic acid, i.e., a permeation enhancer.

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[7] U.S. Patent 7,214,381 B2, issued May 8, 2007, to Carrara et al.

Hwang discloses a transdermal matrix patch comprising huperzine dissolved in a pressure-sensitive polyacrylate adhesive (FF8-10) which releases huperzine at a rate of 1.39 (± 0.15) μg/cm^2/h over a 7 day period (FF11). In addition, Hwang teaches that "[t]he permeation rate required to achieve the therapeutic levels of [huperzine] by transdermal delivery is calculated to be 4.2 μg/cm^2/hr if a 10 cm^2 patch is used" (FF12), which is well within the "about 0.01 μg/cm^2/hr to about 15 μg/cm^2/hr" therapeutic range disclosed in Appellants' Specification (FF7), and Hwang further teaches that a permeation enhancer can be used to increase the skin permeability of huperizine to therapeutic levels if desired (FF12). Venkateshwaran discusses various adhesive polymers and permeation enhancers (FF13), and describes transdermal matrix patches containing an acrylic adhesive and the permeation enhancer lauryl lactate (FF14).

The Examiner acknowledges that Hwang does not explicitly teach "the blood plasma levels of huperzine provided by the transdermal system" (Ans. 4) or the "specific permeation enhancer as instantly claimed" (*id.*), but notes that

> [Hwang] disclosed the amount of the drug used in the transdermal patch in acrylate adhesive is . . . 2.25% (table 2), and applicants disclosed 1-20% huperzine in their formulations (examples). Therefore, [Hwang] teaches the same claimed adhesive, same drug in the same amount, and further teaches permeation enhancer. . . . Further applicants disclosed in pages 21-23 that the claimed plasma level is achieved by permeation rate of huperzine to the skin between 0.01 to 15 μg/cm^2/hr, and the reference teaches effective permeation rate more than 1.46 μg/cm^2/hr . . .

(*id.* at 6-7).

The Examiner concludes that it would have been obvious "to provide a transdermal drug delivery system to deliver huperzine to treat patients suffering from [Alzheimer's disease] wherein the system comprises polyacrylate adhesive and . . . [a] permeation enhancer as disclosed by [Hwang]" (Ans. 5). The Examiner further concludes that it would have been obvious to use a fatty acid ester of lactic acid as the permeation enhancer because Venkateshwaran describes an "adhesive matrix [which] comprises acrylic . . . adhesive[ ] and permeation enhancer including fatty acid esters including lauryl lactate" (*id.* at 4).

The Examiner's conclusion that the claimed invention would have been obvious over the prior art is supported by the evidence of record, and we are not persuaded otherwise by Appellants' arguments.

Specifically, Appellants contend that "numerous examples of third party teachings" (App. Br. 14) establish that "[t]ransdermal drug delivery is a very complex and delicate art" and "the identification of specific permeation or penetration enhancers for specific active agents is an extremely difficult and complicated challenge" (*id.* at 13), difficult to predict, and "must be carefully analyzed and demonstrated by empirical work" (*id.* at 17). Appellants contend that Venkateshwaran "provides extremely limited teachings or correlation of specific active agents with specific permeation enhancers and provides no teaching correlating fatty acid esters of lauryl alcohol with antiparkinsonism drugs, let alone huperzine" (*id.* at 13). Appellants contend that, "based on the knowledge in the art, one of ordinary skill in the art would not have had reason to combine the cited references nor would they have had reasonable expectations of success in forming such a combination" (*id.* at 16).

We have carefully considered Appellants' arguments, but are not persuaded that the Examiner erred in concluding that the claimed invention would have been obvious to one of skill in the art. While the evidence of record generally supports Appellants' assertion that it is not predictable ahead of time which, if any, permeation enhancers would be compatible with Hwang's huperzine/polyacrylate matrix patch, the evidence of record also shows that it was considered routine in the art to identify compatible combinations and relative amounts of permeation enhancers empirically (FF15-16). Moreover, Hwang suggests that a permeation enhancer can be included in the transdermal formulation to achieve a therapeutic dosage, and Hwang's disclosed therapeutic dosage is within the range asserted in the present Specification to be therapeutic (FF7, FF11, FF12).

In any case, even if we accept for the sake of argument that identifying a permeation enhancer ideally suited for Hwang's matrix patch would have required evaluating a large number of candidates, that doesn't mean that one of ordinary skill in the art wouldn't have had a reasonable expectation of identifying a compatible permeation enhancer through routine, empirical experimentation. By the same token, it doesn't mean that the identity of a permeation enhancer identified by such routine experimentation would have been in any way unexpected or surprising - especially as Venkateshwaran shows that acrylate polymer adhesives are conventionally combined with permeation enhancers like lauryl lactate (FF13-14).

Nor is there anything in Appellants' Specification that indicates otherwise - indeed, Appellants' Specification teaches on one hand that "[a] wide range of known permeation enhancers have been found to enhance the

delivery of huperzine" (FF5) and, and on the other hand, that "no enhancer is necessary in order to achieve the desired blood plasma levels in many instances," thus, a transdermal formulation may "consist essentially of an amount of huperzine sufficient to achieve a huperzine blood plasma level of from about 0.1 to about 30 ng/ml admixed with an inert carrier" (FF6).

CONCLUSION

The Examiner's conclusion that the claimed invention would have been obvious over the prior art is supported by the evidence of record.

The rejection of claims 81-84, 86, 102, and 103 under 35 U.S.C. § 103(a) as unpatentable over Hwang and Venkateshwaran is affirmed.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED

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